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ABSTRACT

Background: Increasing our knowledge of past influenza pandemic patterns in different regions of the world is crucial to guide preparedness plans against future influenza pandemics. Here, we undertook extensive archival collection efforts from three representative cities of Peru–Lima in the central coast, Iquitos in the northeastern Amazon region, Ica in the southern coast–to characterize the temporal, age and geographic patterns of the 1918–1920 influenza pandemic in this country.

Materials and methods: We analyzed historical documents describing the 1918–1920 influenza pandemic in Peru and retrieved individual mortality records from local provincial archives for quantitative analysis. We applied seasonal excess mortality models to daily and monthly respiratory mortality rates for 1917–1920 and quantified transmissibility estimates based on the daily growth rate in respiratory deaths. *Results:* A total of 52,739 individual mortality records were inspected from local provincial archives. We found evidence for an initial mild pandemic wave during July–September 1918 in Lima, identified a synchronized severe pandemic wave of respiratory mortality in all three locations during November 1918–February 1919, and a severe pandemic wave during January 1920–March 1920 in Lima and July–October 1920 in Ica. There was no recrudescent pandemic wave in 1920 in Iquitos. Remarkably, Lima experienced the brunt of the 1918–1920 excess mortality impact during the 1920 recrudescent wave, with all age groups experiencing an increase in all cause excess mortality from 1918–1919 to 1920. Middle age groups experienced the highest excess mortality impact, relative to baseline levels, in the 1918–1919 and 1920 pandemic waves. Cumulative excess mortality rates for the 1918–1920 pandemic period were higher in Iquitos (2.9%) than Lima (1.6%). The mean reproduction number for Lima was estimated in the range 1.3–1.5.

Conclusions: We identified synchronized pandemic waves of intense excess respiratory mortality during November 1918–February 1919 in Lima, Iquitos, Ica, followed by asynchronous recrudescent waves in 1920. Cumulative data from quantitative studies of the 1918 influenza pandemic in Latin American settings have confirmed the high mortality impact associated with this pandemic. Further historical studies in lesser studied regions of Latin America, Africa, and Asia are warranted for a full understanding of the global impact of the 1918 pandemic virus.

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1. Introduction

The 1918–1920 influenza pandemic represents a unique epidemiological phenomenon of recent history. During the last few years, there has been increasing interest among the scientific

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community in elucidating the signature epidemiological patterns associated with this pandemic, especially with respect to variation with age, geography and transmissibility [1-3]. A better understanding of these patterns is essential to better prepare for future influenza pandemics.

Quantitative analyses in North America (US [4,5], Canada [6,7], Mexico [8]), Europe (Denmark [9], Spain [10], France [10]) and Asia (Japan [11], Singapore [12] Taiwan [13]) have revealed characteristic features of the 1918–1920 influenza pandemic, including increased mortality rates in young adults relative to seasonal epidemics and the occurrence of multiple pandemic waves over





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Table 1
Distribution of individual all-cause mortality records retrieved from 3 representative cities of Peru

Location	Population size estimate in 1917	Years	Total mortality records	Source
Lima	194,640	1916–1920	46,711	Public Benevolent Institution of Lima
Iquitos	11,466	1915–1921	2,576	Public Benevolent Institution of Iquitos
Ica	70,439	1912–1922	1,749	Public Benevolent Institution of Ica

short periods of time [1]. In addition, available data suggest that senior populations in the US and Europe experienced little or no excess mortality during the pandemic. This phenomenon of "senior sparing" was likely associated with exposure to related influenza viruses in the 19th Century, a concept known as "original antigenic sin", which was described by Francis [14]. Despite recent interest in historical studies, pandemic mortality patterns remain poorly described in many areas of the world, particularly in Latin America, Africa and Asia.

Recent epidemiological surveillance efforts have shed light on the contemporary patterns of influenza circulation in Peru [15–17], but the impact of historical influenza pandemics remains poorly understood. Here, we undertook a detailed historical study of the 1918–1920 influenza pandemic in Peru, a geographically diverse country with a wide variety of ecological systems, including desert coastal areas, temperate highlands, and rainforest, to characterize the age and geographic patterns of the pandemic in this region.

2. Material and methods

2.1. Localities studied

To obtain detailed data about the temporal dynamics of pandemic waves in Peru, we carried out intense data collection efforts in three representative cities of Peru: Lima, Iquitos, and Ica. Lima, the capital of Peru, is located on the central coast of the country and had an estimated population size of 194,640 in 1917. Iquitos, the capital of the Loreto department, is located in northeast Peru in the Amazonian jungle. Surrounded by three rivers, it is the most populous city in the world that cannot be reached by road. By 1880, Iquitos had become a major center of the rubber industry, and its population in 1917 is estimated at 11,466. The city of Ica was founded in 1563 and is located about 300 km south of Lima along the desert coast of southern Peru.

2.2. Data sources

We manually retrieved a total of 52,739 mortality records from local Public Benevolent Institutions or regional archives (Table 1). For each death record, we manually compiled the age, gender, cause, and exact date of death. Original documents were manually converted to electronic format.

Lima had reliable historical records; however, cause of death and age were either missing or not legible for the great majority of records in the other two cities. Analysis of the archival data from Ica suggests a substantial under-reporting of deaths, as baseline total death rates in pre-pandemic years were more than an order of magnitude lower than in Iquitos or Lima. This could be explained by the presence of a substantial number of informal cemeteries in rural areas at that time. In consequence, the Ica data was only used to illustrate the timing of the 1918 pandemic, rather than to quantify its mortality impact.

2.3. Estimation of excess mortality attributable to influenza

To estimate the mortality attributable to the influenza pandemic during 1918–1920, we calculated excess mortality for each city, pandemic wave, age group, and mortality outcome (respiratory deaths and all-cause), using a combination of previous approaches [8,9,18–20]. First, we identified influenza pandemic periods by fitting a cyclical seasonal linear regression model to respiratory mortality after excluding months with increased respiratory mortality (above 75 percentile of mortality) [9,18,19]. Influenza pandemic periods were defined as the months when mortality exceeded the upper limit of the 95% confidence interval on the model baseline. This approach produced a period of significant excess respiratory mortality during November 1918–January 1919 in all three cities, and a recrudescent period of pandemic activity in 1920 in Lima and Ica.

In the second step, we calculated excess mortality as the observed mortality during pandemic months minus the average mortality observed in corresponding non-pandemic months of surrounding years (1915–1921). We summed the excess deaths above the model baseline during each pandemic period identified during 1918–1920 to estimate the mortality burden of the pandemic. Similar "empirical" methods have been used in past research [8,20] and are particularly well-suited to mortality data with weak seasonality, as in Peru (Fig. 1).

Finally, we calculated the relative risk of pandemic death, defined as the ratio of excess mortality during pandemic periods to the expected mortality in the absence of influenza virus activity, given by the model baseline. The relative risk measure has been shown to facilitate comparison between age groups and locations, which have different baseline risks of death [19,21].

2.4. Estimation of transmission potential

The basic reproduction number (R_0) measures the potential of an infectious disease to spread in a theoretical setting and is defined as the average number of secondary cases generated by a primary case during the initial epidemic period in an entirely susceptible population [22,23]. A related quantity is the effective reproduction number, R, which is the average number of secondary cases per primary case in the presence of pre-existing immunity and/or public health interventions [3]. In the case of influenza pandemics, we can expect little or no residual immunity, and hence R is a good approximation of R_0 (assuming no intervention). We estimated the reproduction number, R, using a previously-established method that relies on the growth rate during the initial exponential phase of the pandemic, as in [3,8,24]. We estimated the growth rate (r) by fitting an exponential function to the initial increase in the daily number of respiratory deaths [8,25]. Reproduction number was calculated by using our estimates of the growth rate and assuming exponentially distributed latent and infectious periods or a fixed generation interval (delta distribution) [24].

We also evaluated the sensitivity of *R* estimates to the choice of mortality indicator and compared estimates derived from crude respiratory deaths and excess respiratory deaths above the baseline.

Because of the uncertainty associated with the generation interval for influenza, we considered two extreme values of the generation interval used in past research: a short interval of three days (where the latent and infectious periods were both set to 1.5 days) [24,26,27] and a longer interval of 6 days (latent period = 1.9 days and infectious period = 4.1 days) [5,28]. We have used the same approach in prior studies of the 1918 influenza pandemic in Copenhagen [9] and two Mexican cities [8].

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